Am J Cancer Res 2023;13(8):3799-3821
www.ajcr.us /ISSN:2156-6976/ajcr0151906

Review Article

Role of the RNA-binding protein family in gynecologic cancers

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Received June 25, 2023; Accepted August 15, 2023; Epub August 15, 2023; Published August 30, 2023

Abstract: Gynecological cancers pose a threat to women's health. Although early-stage gynecological cancers show good outcomes after standardized treatment, the prognosis of patients with advanced, met-astatic, and recurrent cancers is poor. RNA-binding proteins (RBPs) are important cellular proteins that interact with RNA through RNA-binding domains and participate extensively in post-transcriptional regulatory processes, such as mRNA alternative splicing, polyadenylation, intracellular localization and stability, and translation. Abnormal RBP expression affects the normal function of oncogenes and tumor suppressor genes in many malignancies, thus leading to the occurrence or progression of cancers. Similarly, RBPs play crucial roles in gynecological carcinogenesis. We summarize the role of RBPs in gynecological malignancies and explore their potential in the diagnosis and treatment of cancers. The findings summarized in this review may provide a guide for future research on the functions of RBPs.

Keywords: Gynecological cancer, RNA-binding protein, ovarian cancer, cervical cancer, endometrial cancer

Introduction

Three major gynecological malignancies, cervical cancer (CC), endometrial cancer (EC), and ovarian cancer (OC), account for approximately 15% of the global female cancer incidence and 12.4% of global female mortality; thus, they represent serious threats to women's health and lives [1]. Although the five-year OS is better for early-stage gynecological cancers, patients with advanced, recurrent, and metastatic advanced gynecological malignancies have limited treatment options. Therefore, new biomarkers for the early diagnosis of gynecological malignancies and potential therapeutic targets must be identified.

The post-transcriptional regulation of gene expression is mainly influenced by RNA-binding proteins (RBPs) and microRNAs (miRNAs). RBPs are a class of proteins that can bind to the RNA domain or nondomain and affect the fate or function of RNA [2]. RBPs broadly control every stage of the RNA life cycle, including RNA transcription, splicing, editing, degradation, and translation, thereby altering the quantity, structure, and function of RNA [3, 4]. For example, RBPs can recognize and bind to specific sequences or structural elements, such as splicing sites, degradation signals, or translation initiation codons, to promote or inhibit the corresponding responses. RBPs can also help RNA form complex three-dimensional structures, such as ribosomes or splicosomes, to participate in protein synthesis or gene expression regulation. RBPs can also change their affinity or selectivity through phosphorylation, ubiquitination, or acetylation to adapt to different physiological or pathological conditions. Thus, RBPs play a wide range of roles in both physiological and pathological processes, such as cell differentiation, stress response, tumorigenesis, and neurodegenerative diseases [3, 5]. Abnormal RBP expression has been observed in many cancers and exerts different bio-logical effects, such as on cell proliferation, invasion, migration, and stemness [6-9]. In this article, we review the function of RBPs in binding to RNA, binding modes of RBPs with RNA, methods of investigating RBP interactions with RNA, and

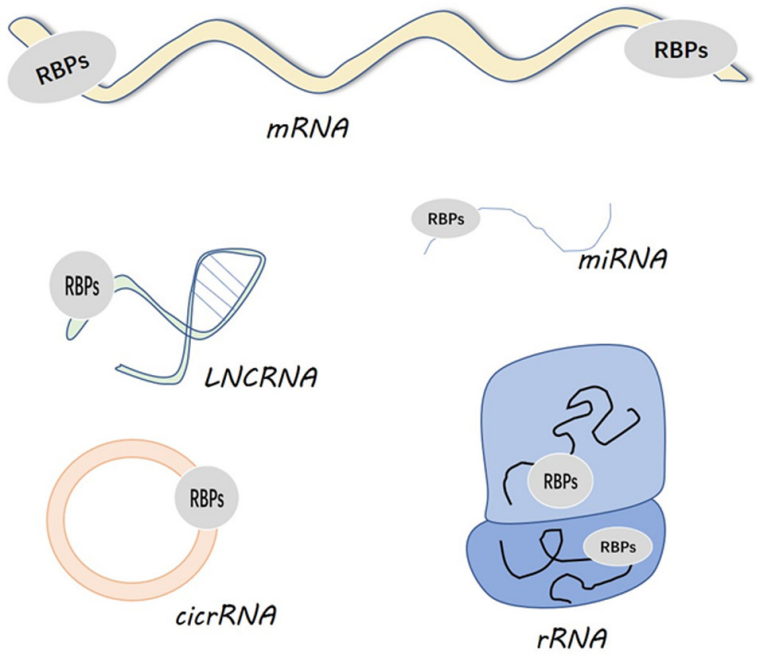

Figure 1. RBPs bind to different kinds of RNAs.

role of RBPs in the post-transcriptional regulation of mRNA in cancer, and the focus is on relevant studies on RBPs in gynecological cancers. This review collates important data that may be used as a guide for future research on the functions of RBPs.

RBPs bind to different kinds of RNAs

RBPs bind to different types of RNA to perform various biological functions (**Figure 1**), including regulating RNA metabolism, assisting RNA function, and adapting to the cellular status or environmental conditions. RBPs regulate RNA metabolism by participating in RNA transcription, splicing, editing, degradation, trans-location, and translation. RBPs can act as cofactors or effectors of RNA, thereby helping RNA accomplish its specific functions. RBPs can also regulate their interactions with RNA according to signals inside and outside the cell to dynamically regulate RNA metabolism and function.

Researchers have found that nearly 50% of RBPs play a role in mRNA metabolic pathways, while the rest are involved in multiple metabolic processes involving non-coding RNA (ncRNA) [10]. In mRNA, RBPs can bind to the 5' cap or 3' poly(A) tail of mRNA to protect it from degradation by ribonucleases and to the coding or non-coding regions of mRNA to alter the splicing pattern or translation efficiency [11]. In tRNA, RBPs can also recognize and cleave introns in tRNA precursors and add or remove chemical modifications on tRNAs, such as methylation or acetylation [10]. In rRNA, RBPs can help rRNA form the correct secondary structure and assist rRNA in assembling with ribosomal proteins into subunits, or play catalytic or assisting roles on the ribosome [12]. In miRNA, RBPs can recognize and cleave the circular structure in the precursor of miRNA and help miRNA move from the nucleus to the cytoplasm, or protect or degrade miRNA [13]. Moreover, RBPs can form complexes with miRNAs or their target mRNAs, thereby enhancing or reducing the affinity of miRNAs for mRNAs. They can also interfere with or promote the formation and function of miRNA-induced silencing complexes [13]. In addition, RBPs can transport miRNAs into the nucleus and interact with transcription factors or chromatin-modifying enzymes to affect the promoter activity or epigenetic status of specific genes [14]. In lncRNA, RBPs play crucial roles in regulating various processes such as transcription, splicing, transport, degradation [15, 16]. After binding to lncRNA, RBPs change their own activity or stability, thereby affecting the expression or function of other RNAs or proteins. The complexes formed by RBPs and lncRNA are involved in biological processes such as nuclear paraspeckles, ribosome assembly, chromatin remodeling [15]. RBPs promote the formation of circRNA by bridging the splice acceptor and donor sites closer together, leading to cyclization. The interaction between circRNA and RBPs has a dual effect: it regulates the location, stability, and function of circRNA within cells, and it modifies the activity or stability of RBPs, which in turn influences the expression or function of other RNAs or proteins [17]. Furthermore, the complexes composed of circRNA and RBPs are implicated in biological processes such as transcription, splicing, translation, and signal transduction [18].

Binding patterns of RBPs to RNA

RBPs perform various functions to maintain cellular homeostasis. These rich functions suggest that RBPs have corresponding diversity in the structures responsible for recognizing RNA. Conventional RBPs are composed of several basic domains and their intermediate catalytic domains, which are arranged in various ways to bind to specific RNA sequences or structures to perform different functions [19]. RNA-binding domains (RBDs) are either spherical or non-spherical [2]. Common RBDs include RNA recognition motifs (RRMs), K homology (KH) domains, double-stranded RBDs, and zinc finger domains [19]. RRMs are the most common RBDs. The interactions between RBDs and RNA involve many mechanisms, including hydrogen bonds and van der Waals forces, which mainly exist on bases, sugar loops, and RNA skeleton phosphates; salt bridges (ionic electrostatic interactions), such as negatively charged RNA skeleton phosphates and positively charged Lys/Arg residues on proteins; and aromatic stacking and hydrophobic interactions, such as interactions between bases and Trp/Tyr/Phe/His on proteins.

With increases in proteomics research, the number of discovered RBPs has doubled; however, hundreds of RBPs have been found to be lacking typical RBDs. They do not have a fixed three-dimensional structure or form a protein structure when they bind to RNA [2]. For example, the intrinsically disordered regions (IDRs) of unconventional RBPs mediate the binding of RBPs to RNA [20, 21]. In addition, certain IDRs have highly specific RNA-binding capacities while others non-selectively bind to RNA [22]. The mechanisms underlying the dynamic composition and uncharacterized structure of IDRs are unknown currently, although IDRs are dominant in more than 20% of RBPs [23]. RNA can also be folded into 3D structures to form complex surfaces that can bind to RBPs to form RNA-protein complexes with complementary shapes [24]. In addition, RNA interaction interomics studies have identified metabolic enzymes as RBPs [25]. Metabolic enzymes are enzymes whose expression profiles are controlled by cellular properties, resulting in tissue metabolic specialization. Metabolic enzymes can bind to RNA and participate in the post-transcriptional regulation of mRNA [26], and the binding of RNA to these enzymes can also regulate the activity and localization of these enzymes [27]. Similar to conventional RBPs, non-conventional RBPs bind to RNA via electrostatic interactions, hydrogen bonding, hydrophobic interactions, and base stacking [2], and they can also recognize specific RNA sequences or structures that play important roles in cell function and disease genesis.

In summary, RBP domains are abundant, and hundreds of RBP domains have yet to be characterized. Their diversity, uniqueness, and extensive roles in various biological processes are remarkable.

Methods of studying RNA-protein interactions

Different researchers have reported different estimates of the total number of RBPs, although it is generally believed that the number of RBPs ranges from 1000 to 2000, which corresponds to more than 7.5% of the protein-coding genes in the human genome [28-30]. Large-scale high-throughput sequencing technologies and mass spectrometry have been used to identify mRNA targets and the functional effects of RNA-protein interactions [31]. With the continuous deepening of research on RNA, re-searchers have found that RNA can act as a mediator of genetic information transmission, and many types of RNA molecules can play a direct role. Studying the binding of RNA to its target molecules is an important step for exploring RNA functions. RBPs are important targets of RNA and are crucial for exploring RNA functions.

The most commonly used methods for studying RNA-protein interactions are crosslinking immunoprecipitation (CLIP) and RNA immunoprecipitation (RIP). RIP is the most common technique for studying RNA-protein interactions, and it uses anti-bodies against the target protein to precipitate the corresponding RNA-protein com-plex and then isolates and purifies the RNA bound to the complex for analysis [32]. This technique is a genome-wide detection technology; however, it is prone to false-positive and false-negative results owing to differences between the lysis conditions used in the experiment and physiological conditions. Therefore, the results obtained from RIP often require further validation. The shortcomings of RIP can be optimized using crosslinking tech-

niques. Natural RNA-protein interactions can be stabilized in cells by covalent bonding through ultraviolet (UV) irradiation-induced crosslinking and chemical-induced crosslinking. The CLIP technique analyzes the binding sites of RNA-protein interactions by combining UV crosslinking and immunoprecipitation. In 2008, CLIP combined with high-throughput sequencing was used to create a genome-level map, and since then, this technology has been applied more widely, al-lowing for the discovery of many binding sites for RBPs [33]. Researchers have since improved CLIP according to their research needs, and several new techniques have been derived from CLIP, such as individual-nucleotide resolution CLIP [31], photo-activable ribonucleoside enhanced CLIP [34], and enhanced CLIP [35]. Both CLIP and RIP are in vivo methods that are influenced by factors such as the cell type and growth state. In vitro methods can help avoid these problems. Existing in vitro high-throughput screening technologies include RNA-compete, SEQRS, RBNS, RNA-Map, HiTS-RAP, and RNA-MITOMI technology [36]. However, the experimental conditions of such analyses are often different from the physiological conditions and thus cannot fully reflect the interactions under physiological conditions. In addition, approaches that label RBPs by modification or editing and then identify endogenous RBPs are relatively novel and include TRIBE [37], RNA tagging [38], and STAMP [39]. These methods mainly involve enzyme labeling of RBPs and then identifying RBPs and their targets using this label. They have the advantage of reducing the number of operational steps and revealing the functions of RBPs in cell subsets using a small number of cells. As different RBP modifications are possible, this research method is expected to be further developed.

RBPs play important roles in various biological processes. To reveal the RBPs bind to specific RNA, the proteins centered on RNA must be captured. RNA interactome capture is performed in vivo and in vitro. In vitro, RNA can be modified using biotin or small-molecule analogs and immobilized on magnetic beads, which are then eluted to obtain the corresponding proteins [40]. In vivo, covalent crosslinking can be used to immobilize RNA-protein complexes, which can then be bound to the target RNA using markers for the analysis of downstream proteins [40]. These techniques include capture hybridization analysis of RNA targets, chromatin isolation using RNA purification techniques, and RNA antisense purification techniques [41, 42]. UV and formaldehyde are relatively mainstream covalent crosslinking methods, and researchers have developed new crosslinking methods, such as psoralen photocrosslinking RNA under UV light [43] and BirA/APEX-mediated proximity labeling [44]. When combined with different enrichment strategies, these crosslinking methods have enriched RBPs via various techniques, including using the poly(A) tail of mRNA [20], click reactions with alkyne uridine analogs [45], and the solubility preference of RNA-protein complexes in organic solvents [46]. In addition, proximity proteomics has been applied to RNA-protein interactions centered on RNA in living cells, which do not require any form of crosslinking.

With the discovery of an increasing number of RNA-protein interactions, a series of associated bioinformatics prediction techniques have also been developed rapidly. Prediction tools are based on known RNA sequence characteristics in RNA-protein interactions, including MEME, RBP map, SeAMotE, and RNA context [36]. A class of tools has also been developed that predicts whether RNA can be bound by analyzing protein surface structure characteristics, and these tools include Struct-NB, PRIP, SPOT-Seq, and OPRA [36]. With the continuous development of RBP research tech-nologies and the enrichment of relevant data, prediction algorithms can more accurately predict the binding sites and modes between RBPs and RNA.

RBPs regulate mRNA in cancer

Many studies have identified RBPs as key factors in cancer development and progression and shown that their abnormal expression is associated with poor prognosis. Many cancer-related proteins are encoded by mRNAs, and RBPs are the major regulators of their expression [47]. To date, approximately half of the identified RBPs are thought to have direct or indirect effects on each step of the mRNA life cycle [10]. Here, we describe in detail the effects of RBPs on alternative splicing, polyadenylation, subcellular localization, stability, and translation of mRNA in cancer.

RBPs regulate the alternative splicing of mRNA

Alternative splicing of mRNA is an important post-transcriptional regulatory mechanism. Alternative splicing is a process in which different combinations of exons within a pre-mRNA are selected and joined together, leading to the generation of multiple mRNA isoforms from a single gene. This process allows for the production of various protein isoforms with distinct functions and properties. The splicing process is orchestrated by the spliceosome, a complex of proteins and small nuclear RNAs (snRNAs). RBPs play a crucial role in regulating alternative splicing by binding to specific sequences in pre-mRNA called splicing regulatory elements (SREs) [48]. Different RBPs can synergistically or antagonistically regulate specific alternative splicing events to form complex splicing network [48]. The role of RBPs in alternative splicing is related to their binding sites, domains, interaction factors, and cellular environment [48]. Some RBPs are known to be alternative splicing regulators, such as heterogeneous nuclear ribonucleoprotein (hnRNP), serine-rich and arginine-rich protein (SR protein) [49], Quaking (QKI) protein [50], RNA-binding motif protein 10 (RBM10), and RNA-binding motif protein 24 (RBM24) [51].

In cancer, aberrant alternative splicing events can lead to the production of abnormal or oncogenic protein isoforms. These altered proteins can contribute to tumor growth, invasion, and evasion of cell death, thereby promoting cancer progression. For instance, certain RBPs can promote the inclusion or exclusion of specific exons in cancer-related genes, leading to the expression of oncogenic isoforms. In many cancers, the dysfunction of hnRNP and SR proteins leads to abnormal splicing and the formation of transcriptional isoforms that can promote proliferation or inhibit apoptosis [52]. In normal cells, QKI selectively skips exon 12 of NUMB mRNA by competing with the core splicing factor SF1, producing NUMB isoforms without exon 12, negatively regulating the Notch signaling pathway, and inhibiting cell proliferation [53]. In non-small cell lung cancer, QKI is one of the most commonly downregulated splicing molecules, and its downregulation is significantly associated with poor prognosis [53]. Xu et al. [54] reported that ERα is an unconventional RBP and demonstrated that ERα binding to RNA mediates the alternative splicing of XBP1 mRNA and translation of eIF4G2 and MCL1 mRNA, which facilitates the survival of breast cancer cells under stress conditions and maintains tamoxifen resistance [54]. RBM10, a splicing factor, promotes exon 9 skipping of NUMB mRNA under normal conditions, resulting in a NUMB isoform that can inhibit Notch activity and proliferation [55]; however, it is downregulated in lung adenocarcinoma. Qiao et al. [56] found that RALY, which is a member of the hnRNA family, promotes cell proliferation in hepatocellular carcinoma by cooperating with SF3BS to reduce MTA1-S levels. Ma et al. [57] overexpressed CELF6, which is a non-canonical RBP, in lung cancer A549 cells and found that it regulated the expression and alternative splicing of cancer-related genes, especially those involved in apoptosis and the P53 signaling pathway. Yan et al. [58] found that RBMX, which is a widely expressed nu-clear RBP, can inhibit tumorigenicity and progression of bladder cancer through hnRNP A1-mediated alternative splicing of PKM. Ye et al. [59] created the novel technique Capture RIC-seq to capture specific RBP-mediated RNA-RNA in situ spatial in-teractions. Using this technique, the researchers mapped the spatial RNA interactions mediated by PTBP1, hnRNPA1, and SRSF1. This map revealed a new mechanism by which PTBP1 inhibits splicing by dimerizing the formation of RNA rings across the alternative exon between introns on both sides and facilitates alternative exon splicing by mediating the formation of RNA rings within introns on one side. Can-cer-associated splicing of quantitative trait loci can disrupt the affinity of the PTBP1 protein for RNA target sites and affect the formation of RNA loops, thereby leading to changes in splicing isoforms and abnormal proliferation of cancer cells. Thus, alternative splicing plays a significant role in normal development. Disruption of these processes can lead to cancer development. Cancer cells present general, cancer-specific, and subtype-specific alterations in splicing processes that mark cancer progression and have potential prognostic value [60].

RBPs regulate the alternative polyadenylation of mRNA

Polyadenylation is the process of adding a poly(A) tail at the 3' end of mRNA molecules.

This poly(A) tail is crucial for mRNA stability, export from the nucleus to the cytoplasm, and efficient translation into proteins. Alternative polyadenylation (APA) is also a post-transcriptional regulatory mechanism that can influence gene expression by altering the 3' untranslated region (UTR) of mRNA or the length of the 3' UTR through adding poly(A) tails at different locations in the RNA 3' UTR to regulate mRNA stability, subcellular localization, and translation efficiency [61]. Different mRNA isoforms may contain or lack cis-acting elements that bind to RBPs, thereby altering mRNA transport, stability, localization, and translation [61, 62]. The role of RBPs in APA is related to the binding sites, domains, interaction factors, and cellular environment [61, 62]. Several APA regulators have been reported, including the QKI protein [63], cytoplasmic polyadenylation element binding (CPEB) protein family he role of alternative polyadenylation in cancer progression, and cleavage factor Im (CFIm). These RBPs exhibit biological functions by participating in cell differentiation and development [63, 64]. For example, in liver cells, QKI-7 has a specific affinity for microRNA-122. QKI-7 forms a ternary complex with GLD-2 and Ago2 to promote the polyadenylate of microRNA-122, thereby improving the stability of microRNA-122 and controlling the aging of hepatocytes [63].

In cancer, alterations in polyadenylation processes can lead to changes in mRNA stability and translation efficiency. Dysregulated polyadenylation can result in the production of unstable mRNAs, leading to reduced expression of tumor-suppressor genes or increased expression of oncogenes. Additionally, changes in polyadenylation site usage can affect the stability and localization of mRNA transcripts, leading to oncogenic changes in gene expression. 3' UTR shortening is primarily regulated by the splicing factor CFIm complex, which includes the CFIm25 and CFIm68 proteins. In glioblastoma, CFIm25 deletion can reduce the use of the distal poly(A) sites of target genes, resulting in a large number of genes with shortened 3' UTR sites or lacking miRNA-binding inhibitory sites. This promotes the increased expression of genes associated with cell proliferation (such as cyclin D1) and carcinogenesis [65]. Pieraccioli et al. [66] revealed that MYC upregulates the expression of the RBP Sam68 and exonuclease XRN2 in prostate cancer cells. The Sam68/XRN2 complex accelerates cell cycle progression via APA, thereby promoting cancer cell proliferation. CPEB4, a member of the CPEB family, is upregulated in pancreatic cancer and promotes the abnormal translation and overexpression of mRNA by promoting poly(A) tail extension of the tissue plasminogen activator mRNA, thereby promoting tumor growth, invasion, and angiogenesis [67]. In conclusion, APA plays a role in cancer by activating the expression of various oncogenes and tumor suppressor genes [68]. These APA events have been found to be associated with the prognosis, recurrence, pathological subtype, and stage of multiple cancers [69].

RBPs regulate the stability of mRNA

The stability of mRNA molecules is crucial for controlling gene expression levels. mRNA stability is regulated by a delicate balance between factors that promote mRNA degradation (such as endonucleases and exonucleases) and factors that protect and stabilize mRNA molecules. RBPs regulate mRNA degradation or stabilization by interacting with specific structural elements of mRNA [70, 71]. These structural elements include the 5' cap, 3' poly(A) tail, coding region, and non-coding region [71]. Different RBPs can promote or inhibit mRNA stability, thus affecting gene expression [71, 72]. Adenylate-uridylate-rich elements (AREs) located in the 3' UTR of certain genes can regulate mRNA stability at the post-transcriptional level. In resting cells, transcripts containing AREs are unstable and can be targeted for degradation by deadenylation, a process that requires the involvement of ARE-binding proteins. In general, oncogenic factors are enriched in AREs. Various RBPs affect mRNA stability, including HuR, AUF1, TTP, and CUGBP1.

In cancer, RBPs can influence mRNA stability to control the expression of genes involved in cancer-related processes, such as cell cycle regulation, apoptosis, and angiogenesis. Dysregulation of RBPs can lead to increased stability of oncogenic transcripts, promoting cancer cell survival, proliferation, and migration. For example, HuR is overexpressed in various cancer types and can enhance the stability of ARE-rich transcripts such as the cell cycle regulators CCNA1, CCNB1, CCND1, and CCNE1, thereby promoting cancer cell proliferation [73]. hnRNP

D, also known as AU-rich element RNA-binding protein 1, is composed of four family proteins, namely, P37, P40, P42, and P45, which are alternative splice isoforms with different molecular weights. Overexpression of P37 in transgenic mice results in the spontaneous formation of tumors owing to the accumulation of various tumor-related transcripts (CCND1, FOS, and MYC) [74]. AUF1 is associated with mRNA instability. However, in some cases, AUF1 also plays a role in stabilizing mRNA. Moreover, AUF1 also exerts anti-tumor effects by reducing the stability of mRNA for anti-apoptotic protein BCL2 and inflammatory factors GM-CSF, IL-6, IL-10, and TNF-α [4]. HuR and AUF1 competitively bind to ARE-containing mRNA and produce antagonistic effects, although the final outcome depends on the abundance, stress conditions, and subcellular localization of each RBP [73]. TTP is also an RBP that binds AREs and can promote mRNA degradation [72, 75]. In cancer, TTP expression is usually downregulated, which in-creases the stability of the mRNAs of some oncogenes or tumor suppressor genes [72, 75]. For example, in hepatocellular carcinoma, TTP deficiency can increase mRNA stability for inflammatory factors and cytokines, such as IL-6, TNF-α, and CXCL10, thereby promoting liver inflammation and tumorigenesis [75]. The RBP CUGBP1 can increase the stability of survivin mRNA, thereby enhancing its expression in esophageal cancer cells, and the apoptosis suppressor protein Survivin is overexpressed in various cancers and correlated with malignancy and prognosis. Musashi (MSI) is an RBP that is selectively expressed in neural, epithelial, and hematopoietic cells, and it deter-mines cell fate at several levels, including maintaining stemness and differentiating stem cells. MSI is upregulated in many cancers, including colorectal cancer, lung cancer, pancreatic cancer, glioblastoma, and leukemia. MSI1 and MSI2 bind together to regulate mRNA stabilization and translation in oncogenic signaling pathways [76].

RBPs regulate the translation of mRNA

Regulation of mRNA translation can serve as another layer of gene transcription control. RBPs can modify the translation of a set of transcripts to meet the actual protein requirements of cells [77] and regulate mRNA translation by binding to the 5' UTR and 3' UTR of mRNA. The mechanisms by which RBPs regulate mRNA translation are diverse. For example, eIF4E promotes mRNA translation by binding to the 5' cap of mRNA and hnRNP C inhibits mRNA translation by binding to the 3' UTR of mRNA [78].

Aberrant RBP expression affects mRNA translation in cancer [79]. For example, hnRNPA1 can regulate mRNA translation by binding to the 5' UTR of mRNA, thereby affecting the proliferation and invasion of cancer cells [80]. CPEB4 promotes the growth, invasion, and angiogenesis of tumor cells by promoting the APA of tissue plasminogen activators, leading to abnormal mRNA translation and overexpression [67]. In addition, RBPs such as HuR, TIA1, and TTP can affect the proliferation, metastasis, and apoptosis of tumor cells by regulating mRNA stability and translation [79].

RBPs regulate the subcellular localization of mRNA

RBPs also play major roles in regulating intracellular mRNA localization. By binding to the 3' UTR of mRNA, RBPs connect mRNA to the cytoskeletal molecular motor and transport the ribonucleoprotein complex to a specific location. The localization of RBPs can regulate gene expression in space and time and is important for cells [81, 82]. In addition, RBP localization has different effects on different cells and tissues. For example, in neurons, RBPs regulate synaptic plasticity and memory formation [82]. In muscle cells, RBPs affect muscle development and regeneration [82]. In immune cells, RBPs participate in inflammatory responses and antiviral defense [82]. This mechanism is critical for establishing and maintaining cell polarity, which is often altered in cancer cells [83]. For example, IGF2BP1 expression is upregulated in many primary tumors, such as breast cancer, colorectal cancer, and non-small cell lung cancer tissues, whereas it is downregulated in metastatic cells due to promoter methylation. Downregulation of IGF2BP1 expression interferes with the normal transfer and mRNA localization of some adhesion- and motility-related proteins, such as a-actinin, b-actin, and E-cadherin. Hence, silencing IGF-2BP1 leads to increased instability of focal adhesion, which ultimately makes the cells prone to metastasis and invasion [84].

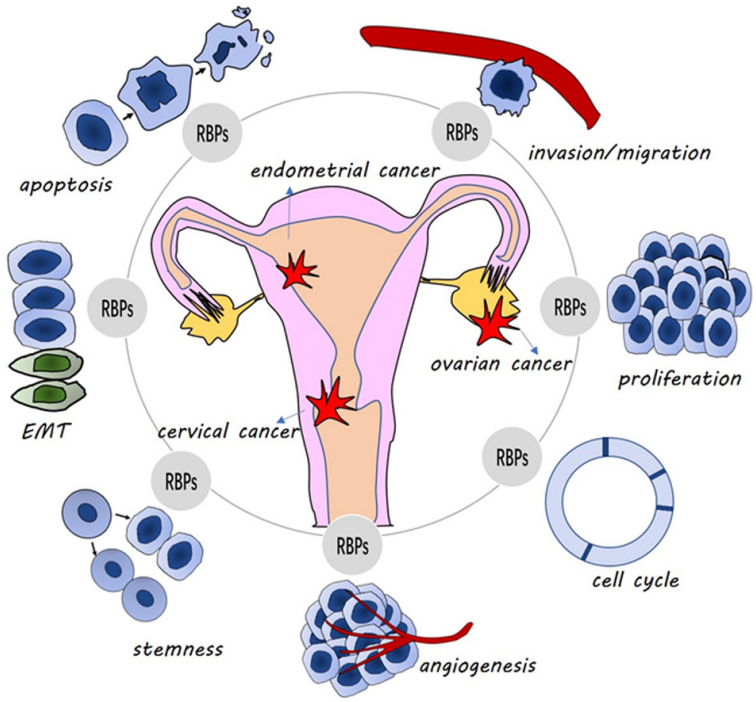

Figure 2. Role of the RNA-binding protein family in gynecologic cancers.

RBPs regulate the methylation of mRNA

In recent years, RNA methylation has been shown to play an important role in post-transcriptional regulation. Proteins related to RNA methylation are a class of RBPs that play important roles in mRNA translation, transcription, and transportation.

m6A is the most abundant RNA modification in eukaryotes and can affect many mRNA metabolic processes that regulate gene expression. m6A-related proteins, as a type of RBP, can recognize and bind to m6A-modified RNA and recruit other proteins to the RNA to determine its fate. For example, FMRP is an RBP that can bind to mRNA with m6A modifications, thereby affecting mRNA transport and translation [85]. m6A-related RBPs play a corresponding role in cancer progression. For example, IGF2BP1 is an m6A recognition protein that interacts with other RBPs to enhance IGF2BP1 recognition of m6A on RNA, thereby increasing mRNA stability and c-Myc expression and promoting tumorigenesis [86]. YTHDF1 is another m6A recognition protein, and HIF-1α-induced YTHDF1 expression drives autophagy and autophagy-related carcinoma progression by promoting autophagy-related gene ATG2A and ATG14 [87].

m5C is another important RNA modification, and its recognition proteins YBXI and ALYREF are both RBPs. YBX1 is highly expressed in bladder cancer tissues. In vivo and in vitro mouse tumorigenesis and metastasis experiments and high-throughput sequencing technology demonstrated that YBX1 promotes HDGF mRNA stability in an m5C-dependent manner and ultimately promotes the proliferation and metastasis of bladder cancer cells [88].

Research progress of RBPs in gynecological cancer

Recurrence and drug resistance in gynecological cancers are challenging problems, and the underlying resistance mechanisms have been extensively studied. The role of RBPs in drug resistance provides a new perspective on the treatment of gynecological cancers. RBPs are involved in multiple oncogenic pathways and may serve as potential targets for gynecological cancer therapy. In summary, RBPs play various roles in gynecological cancers (**Figure 2**), and by fully exploring their functions, the early diagnosis and improved prognosis of these cancers may be resolved.

RBPs in OC

OC is relatively common and has a high mortality rate worldwide. More than 300,000 women are diagnosed with OC each year, and approximately 152,000 women die from OC [1]. OC is known as a “silent” disease because symptoms are not obvious during the early stages. Approximately 75% of patients are diagnosed at an advanced stage. The 5-year survival rate of patients with OC is less than 30%. Currently, no specific biomarkers or effective treatment strategies have been identified for the screening and monitoring of OC. Therefore, it is important to identify effective serum biomarkers for OC screening and develop effective therapeutic approaches for early OC diagnosis. Studies in recent years have shown that RBPs play an important role in the development of OC and

Table 1. The roles of RBPs in ovarian cancer

RBP	Molecular axis	Function	Cellular phenotype/Clinical effect	Referencce
HuR	HuR/TIMM44	Oncogene	Proliferation	[90]
HuR	HuR/NEAT1	Oncogene	Proliferation, invasion	[91]
HuR	HuR/FAM83H-AS1c	Oncogene	Proliferation, invasion, EMT, radiation sensitivity	[92]
HuR	HuR/lncARSR/β-catenin	Oncogene	Proliferation, icnvasion	[93]
HuR	HuR/SOCS7/FOXM1	Oncogene	Proliferation, invasion, migration, chemoresistance	[95]
HuR	HuR/E2F2	Oncogene	Proliferation, invasion, migration	[96]
HuR	Ursolic acid/HuR	Oncogene	Chemoresistance	[97]
LIN28	LIN28/let-7	Oncogene	Proliferation	[98]
LIN28	Unknown	Oncogene	Poor prognosis	[98, 99]
LIN28A	LIN28A/EMT related genes	Oncogene	Invasion, migration	[100]
LIN28B	hnRNPA2B1/LIN28B	Oncogene	Proliferation, invasion, migration	[101]
LIN28A	Propofol/miR-125a-5p/LIN28A	Oncogene	Proliferation, invasion, migration	[102]
LIN28A	PLK4/LIN28A	Oncogene	Poor prognosis	[103]
MSI	Unknown	Oncogene	Poor prognosis	[107, 108]
MSI-2	MSI-2/p21, p27, Bcl-2	Tumor suppressor gene	Paclitaxel sensitivity	[107, 109]
MSI-1	MSI-1/Notch MSI-1/Wnt/β-catenin MSI-1/Hedgehog MSI-1/PI3K/Akt	Oncogene	Proliferation, invasion, migration, chemoresistance	[107]
LARP1	Unknown	Oncogene	Proliferation, stemness, chemoresistance	[110]
LARP1	LARP1/Bcl-2/BIK	Oncogene	Apoptosis, cell survival rate	[111]
SFPQ	Unknown	Unknown	Platinum chemoresistance	[112]
IGF2BP1	IGF2BP1/c-myc	Oncogene	Proliferation	[113]
IGF2BP1	IGF2BP1/SRC/MAPK	Oncogene	Invasion	[114]
IGF2BP2	unknown	Oncogene	Proliferation	[115]
IGF2BP3	IGF2BP3/LIN28B	Oncogene	Proliferation, invasion, migration	[116]
IGF2BP3	IGF2BP3/LIN28B/hCTR1d	Oncogene	Cisplatin chemoresistance	[116]
IGF2BP2	IGF2BP2/circ_0000745	Oncogene	Invasion, stemness	[117]
YTHDF1	YTHDF1/TRIM29	Oncogene	Cisplatin chemoresistance	[118]
YTHDF1	YTHDF1/EIF3C	Oncogene	Proliferation, invasion, migration	[119]
YTHDF2	YTHDF2/miR-145	Oncogene	Proliferation, invasion, migration	[122]
YTHDF2	YTHDF2/FBW7/BMF	Oncogene	Apoptosis	[123]
ALKBH5	ALKBH5/HOXA10/JAK2/STAT3	Oncogene	Proliferation, cisplatin chemoresistance	[124]

may serve as potential targets or biomarkers for OC. In this section, we summarize the mechanisms of action of different RBPs in OC (**Table 1**).

Human antigen R (HuR), also known as embryonic lethal abnormal visual pro-tein1, is an important RBP that is widely expressed in various tissues and plays an important role in maintaining mRNA stability. Similarly, HuR plays a significant role in stabilizing oncogene and tumor suppressor gene. Therefore, when HuR expression changes, cancer-related genes also undergo changes that affect the proliferation, invasion, migration, and apoptosis of cancer cells. Translocase of inner mitochondrial membrane 44 (TIMM44) is a peripheral membrane protein associated with mitochon-drial inner membrane translocase that may regulate the transformation of mitochondrial morphology [89]. TIMM44 upregulation promotes proliferation of OC cells, and HuR overexpression promotes TIMM44 expression and slows its mRNA degradation, thereby promoting the proliferation [90]. In recent years, many studies have shown that long non-coding RNAs (lncRNAs) play important roles in the proliferation, invasion, and apoptosis of cancer cells and are key regulators of many malignancies. NEAT1 is an lncRNA that is mainly enriched in the nucle-

us and a key non-coding RNA that forms and maintains the substructural paraspeckles of the nucleus, and changes in its levels have been reported in various cancers. Chai et al. [91] found that NEAT1 also promotes the proliferation and invasion of OC cells and serves as a target of HuR. Overexpression of HuR enhances NEAT1 expression Therefore, HuR may be involved in ovarian carcinogenesis by regulating the expression of NEAT1. FAM83h-AS1 is an lncRNA that exerts oncogenic effects in many cancers. Dou et al. [92] found that FAM83H-AS1 interacts with HuR and stabilizes HuR in OC cells. Moreover, it can promote the migration, invasion, and epithelial-mesenchymal transition (EMT) of OC cells and reduce cellular sensitivity to radiation by regulating HuR. lncARSR has been reported to be associated with drug resistance in several cancers. Shu et al. [93] found that lncARSR upregulates β-linked proteins in a HuR-dependent manner to promote the proliferation and invasion of epithelial ovarian cancer (EOC) cells. Suppressors of cytokine signaling (SOCS) are a class of proteins involved in the regulation of signal transduction and their abnormal expression or activation is associated with the progression of various human cancers [94]. In high-grade serous ovarian cancer (HGSOC), the expression of SOCS7 is downregulated. Du et al. [95] found that SOCS7 regulates the cell cycle, inhibits HGSOC cell viability and growth, and suppresses tumor growth in xenografts. HuR overexpression counteracts the inhibition of cell proliferation caused by SOCS7 overexpression. FOXM1 is a transcription factor and target of HuR. In HGSOC, FOXM1 overexpression contributes to the proliferation, invasion, migration, and chemoresistance of cancer cells. HUR stabilizes FOXM1 mRNA and plays an important role in regulating FOXM1 expression. Further studies revealed that the expression levels of SOCS7, HuR, and FOXM1 are interrelated and that their interactions affect the proliferation and invasion of OC cells. The E2F family is a transcription group of widely expressed factors. E2F2 is a member of the E2F family that promotes cell proliferation. Zhang et al. [96] found that the E2F2 gene can produce three circular RNAs (circRNAs) in OC cells, one of which is called circE2F2. CircE2F2 expression is upregulated in OC cells and can stabilize E2F2 mRNA by binding to the HuR protein to promote cell proliferation, invasion, and migration. Ursolic acid (UA) inhibits the progression of various cancers. Li et al. [97] constructed the adriamycin-resistant ovarian cancer cell line SKOV3-Adr and found that UA reduces adriamycin resistance in SKOV3-Adr cells. UA has been shown to promote the cytoplasmic nuclear transloca-tion of HuR protein, which decreases the mRNA stability of multidrug resistance 1 gene.

The LIN28 family is a type of RBP that directly acts on mRNA or interferes with the maturation of certain miRNAs to regulate developmental timing and self-renewal of embryonic stem cells. The LIN28 family is consists of two members, LIN28A and LIN28B, which exhibit different expression patterns and functions in different tissues and developmental stages. They have unique structures, including zinc finger and cold-shock RBDs. LIN28 can activate several oncogenes and promote proliferation signaling pathways, such as RAS, MYC and HMGA2, by repressing the expression of the let-7 miRNA family [98]. High LIN28 expression is associated with malignancy and poor prognosis in several cancers [98, 99]. LIN28 plays an oncogenic role in OC. Enriquez et al. [100] found that OC cells expressing LIN28A exosomes upregulate the expression of genes associated with EMT and induce the invasion and migration of HEK293 cells. hnRNPA2B1 is a member of a large family of RBPs that is closely associated with tumorigenesis. Yang et al. [101] found that hnRNPA2B1 knockdown significantly inhibits OC cell proliferation, migration, and invasion. hnRNPA2B1 regulates LIN28B mRNA stability and promotes OC cell proliferation and mobility by enhancing LIN28B expression. This study reveals for the first time that the hnRNPA2B1-Lin28B axis is critical for OC progression. Propofol is a commonly used intravenous anesthetic that acts as an antitumor agent in many cancers. Zeng et al. [102] found that propofol upregulates miR-125a-5p in OC cells and that miR-125a-5p directly inhibits its LIN28A expression to suppress the proliferation, invasion, and migration of OC cells. Polo-like kinases (PLKs) are a family of serine-threonine kinases that participate in various cell-cycle processes, including DNA replication, mitosis, and centrosome maturation. PLK4 plays key roles in centriole replication. He et al. [103] showed that PLK4 and LIN28A are overexpressed in OC tissues and cells and positive-

ly correlated. When PLK4 and LIN28A are coexpressed, EOC has a poor prognosis.

The MSI family are a class of evolutionarily conserved RBPs that regulate mRNA translation and stability, thereby controlling cell proliferation and differentiation. MSI has two homologs: MSI-1 and MSI-2. They are widely expressed in multiple cancers, and their expression levels are associated with poor prognosis [76, 104]. The MSI protein has two RNA recognition motifs (RRM1 and RRM2) that bind to the 3' UTR of the target mRNA [105]. The expression levels of MSI-1 and MSI-2 are negatively correlated with prognosis in OC [106, 107]. MSI-2 regulates paclitaxel sensitivity and increases the sensitivity of OC cells to paclitaxel by inhibiting the expression of p21, p27, and Bcl-2 [106, 108]. MSI-1 regulates multiple signaling pathways, such as Notch, Wnt/β-catenin, Hedgehog, and PI3K/Akt, thereby promoting proliferation, migration, invasion, and drug resistance in OC [106].

La-Related Protein 1 (LARP1) is a highly evolutionarily conserved RBP that is unique to the LARPs family owing to the presence of an additional conserved C-terminal tandem repeat motif, namely, the DM15 region. LARP1 plays a role in regulating mRNA stability and translation. Hopkins et al. [109] found that LARP1 promotes the proliferation of OC cells and maintains the stemness and chemical resistance of cancer stem cells. In addition, it can stabilize the mRNA of the anti-apoptotic gene Bcl-2 while disrupting the mRNA of the pro-apoptotic gene BIK, thereby improving the survival rate of cancer cells. Chen et al. [110] found that the lncRNA LINC01969 is highly expressed in OC tissues and cell lines. LINC01969 competes with mR-144-5p to regulate LARP1 expression, which in turn affects the migration, proliferation, invasion, and EMT of OC cells.

Splicing factor proline/glutamine rich (SFPQ) is an RBP that participates in RNA processing, splicing, and transcriptional regulation. In the treatment of EOC, the sensitivity to platinum-based chemotherapy can guide subsequent treatment and predict prognosis. Pellarin et al. [111] found that SFPQ is significantly involved in platinum-based chemotherapy resistance in EOC cells.

m6A is one of the most abundant mRNA modifications in eukaryotes, and some modification enzymes and m6A recognition proteins are important RBPs. m6A recognition proteins include insulin-like growth factor 2 mRNA-binding protein 1/2/3 (IGF2BP1/2/3), YT521-B homology domain-containing proteins, and hnRNP. The IGF2BP family is an evolutionarily conserved mRNA-binding protein family that regulates mRNA transport and translation by binding to the target mRNA coding region. IGF2BP1 and IGF2BP3 enhance the proliferation, metastasis, migration, and invasion of tumor cells in vivo and in vitro. It has been found that when IGF2BP1 is knocked down, the stability of c-myc mRNA and protein is decreased, thus affecting the proliferation of OC [112]. Bley et al. [113] found that IGF2BP1 regulates SRC kinase activity in OC cells. SRC kinase is a key activator of adhesion disassembly and can initiate EMT. IGF2BP1 promotes OC cell invasion via the SRC/MAPK pathway. Hiramatsu et al. [114] performed gene and protein ontology analyses and found that IGF2BP2 overexpression leads to OC cell proliferation. Hsu et al. [115] found that knockdown of IGF2BP3 and LIN28B reduced the proliferation, invasion, and migration of OC cells. When their ex-pression levels are elevated, they will inhibit the expression of hCTR1d, thus leading to the development of cisplatin-resistant OC. Circular RNAs are important non-coding RNA with high stability and powerful regulatory ability. Wang et al. [116] found that circ_0000745 is highly expressed in OC tissues and cells. Downregulation of circ_0000745 inhibits the invasiveness and stemness of OC cells. IGF2BP2 binds to circ_0000745 and promotes its expression in OC cells.

YT521-B homology domain proteins, including YTH N6-methyladenosine RNA binding protein 1/2/3 (YTHDF1/2/3) and YTH domain containing 1/2 (YTHDC1/2), are another class of m6A recognition proteins that are involved in cancer development. Hao et al. [117] found that YTHDF1-mediated TRIM29 upregulation promotes a stem-like phenotype in cisplatin-resistant OC cells. TRIM29 is a tripartite motif protein that is aberrantly expressed in some cancers. YTHDF1 knockdown inhibits the CSC-like characteristics of cisplatin-resistant OC cells, while TRIM29 overexpression rescues this phenomenon. Liu et al. [118] identified EIF3C as a target of YTHDF1 in OC cells using multi-omics analysis. EIF3 is a subunit of eukaryotic initiation factor 3, which is responsible

Table 2. The roles of RBPs in cervical cancer

RBP	Molecular axis	Function	Cellular phenotype/Clinical effect	Reference
HuR	HuR/circ TICRR/GLUD1	Oncogene	Autophagy	[125]
HuR	BBOX1-AS1/miR-6-361p/HuR/HOXC6	Oncogene	Proliferation, migration, invasion	[126]
HuR	p16/HuR/CDK6/IL1A	Oncogene	Proliferation	[127]
hnRNPs	RALYL/HPV16	Oncogene	Result in HPV-related cervical cancer	[130]
hnRNPs	hnRNPs/HPV	Oncogene	HPV genes expression	[131]
QKI	Unknown	Tumor suppressor gene	Proliferation, apoptosis	[133]
QKI	QKI/miR-774-5p	Tumor suppressor gene	Proliferation, invasion, chemotherapy sensitivity	[134]
QKI	QKI/circSLC26A4	Oncogene	Proliferation, invasion	[135]
La	La/CCND1	Oncogene	Proliferation	[136]
MSI-2	Unknown	Oncogene	Poor prognosis	[137]
MSI-2	MSI-2/Wnt/β-catenin/Notch	Oncogene	Proliferation, migration, invasion	[139]
IGF2BP2	IGF2BP2/circARHGAP12/FOXM1	Oncogene	Proliferation, migration	[140]
IGF2BP3	IGF2BP3/KCNMB2-AS1	Oncogene	Malignant phenotype maintenance	[141]
YTHDF1	YTHDF1/RANBP2	RBM15	Proliferation, migration, invasion	[142]
ALKBH5	ALKBH5/GAS5-AS1/GAS5	Tumor suppressor gene	Proliferation, migration, invasion	[143]
RBM15	RBM15/c-myc	Oncogene	Proliferation	[6]
RBM15	RBM15/JAK-STAT	Oncogene	Proliferation, migration, invasion	[8]

for coordinating interactions between initiation factors and ribosomes. YTHDF1 promotes the proliferation, migration and invasion of OC cells. When YTHDF1 is knocked down, EIF3C overexpression can rescue this tumor-suppressive phenomenon. miR-145, an endogenous miRNA, regulates various biological functions by targeting different genes in OC [119, 120]. Li et al. [121] found that YTHDF2 is a direct target gene of miR-145 in OC cells. The overexpression of miR-145 inhibits the proliferation, migration, and apoptosis of OC cells, whereas the overexpression of YTHDF2 weakens these effects. FBW7 is a tumor suppressor that selectively mediates the ubiquitination and proteasomal degradation of oncogenic proteins. Xu et al. [122] found that FBW7 counteracts the tumorigenic effects of YTHDF2 by inducing the ubiquitination of YTHDF2 and degrading the proteasome of YTHDF2. The interaction between FBW7 and YTHDF2 also promotes protein hydrolysis, which stabilizes the ex-pression of the pro-apoptotic gene, BMF and causes apoptosis. ALYBH5 is an m6A-modified demethylase and an RBP, and it plays important roles in RNA metabolism, including RNA stability, translation, and splicing. Nie et al. [123] found that ALKBH5 interacts with HOXA10 to activate the JAK2/STAT3 signaling pathway, thus promoting the proliferation and cisplatin resistance of EOC cells.

RBPs in CC

In developing countries, the incidence and mortality rates of CC are increasing while the age with the highest incidence is decreasing. Persistent infection with high-risk HPV is a well-known major risk factor for CC. HPV vaccines can prevent CC. However, the clinical management of CC still faces challenges, such as monitoring after treatment for early-stage CC, treatment resistance after recurrence of CC, and poor prognosis for late-stage CC. Therefore, effective biomarkers must be developed for the full management of CC and treatment resistance mechanisms and new therapeutic targets must be identified. An increasing number of studies have demonstrated that RBPs affect the proliferation, invasion, migration, and other functions of CC cells, and participate in cancer drug resistance. Therefore, RBPs may serve as potential tumor markers or therapeutic targets for CC. In this section, we list the relevant research on RBPs in CC (**Table 2**).

HuR, a widely expressed post-transcriptional regulator, is associated with various cancers. It has also been found to be involved in the development of CC. Zhu et al. [124] discovered that circRNA-circTICRR interacts with HuR to stabilize GLUD1 mRNA, thereby inhibiting autophagy in CC cells. Therefore, the interaction between circTICRR and the HuR protein may be a potential target for CC treatment. lncRNA BBOX1-AS1 can also promote HOXC6 mRNA overexpression through HuR to drive proliferation, migration and invasion of CC cells [125]. The Cyclin-Dependent Kinase Inhibitor p16 is an important tumor suppressor gene. However, Li et al. [126] found that p16 exhibits oncogenic

properties in tumors and promoted the proliferation of CC cells through the CDK6-HuR-IL1A axis. Tunisian researchers analyzed the effect of single nucleotide polymorphisms in HuR on the development of CC in Tunisian women and found that it may be associated with susceptibility to CC [127].

HPV16 is the most common type of HPV in cervical cancer [128]. Dhanjal et al. [129] identified an RBP called RALYL, which belongs to the hnRNP C family of hnRNPs. RALYL and hnRNP C1 can bind to the HPV16 early UTR and they can induce HPV16 late L1 mRNA splicing in an HPV16 early 3'-UTR dependent manner. Ultimately, it induces HPV16 late gene expression. In addition, human cells contain a large number of hnRNPs, many of which interact with HPV RNA or regulate HPV gene ex-pression, including hnRNP A1, A2/B1, C1/C2, D, E, H, I, and K [129]. Therefore, hnRNPs are important regulatory factors in HPV-associated CC. RNA binding motif protein 15 (RBM15) is an RNA-binding protein involved in m6A modification and variable splicing regulation of RNA. Nie et al. [6] found that HPV-E6 promoted the expression of RBM15 protein in cervical cancer cells by inhibiting autophagy. RBM15 can enhance the m6A level of c-myc mRNA, resulting in increased expression of c-myc protein, which promotes the proliferation of cervical cancer cells.

QKI is an RBP with a KH domain that belongs to the signal transduction and activation of the RNA protein family. They regulate RNA metabolism, including mRNA splicing and translation. QKI has been demonstrated that QKI is a tumor suppressor [130, 131]. Studies have revealed the role of QKI in CC. Luo et al. [132] found that QKI is downregulated in CC, and QKI overexpression inhibits proliferation and promotes apoptosis of HeLa cells. Tong et al. [133] found that miR-774-5p has a carcinogenic effect on CC cells. However, when mir-774-5p expression is inhibited, QKI expression is significantly increased in the cells. At the same time, the proliferation and invasion abilities of cancer cells decrease, and their sensitivity to chemotherapy increases. This suggests that QKI, as a target gene of miR-774-5p, can inhibit the progression and metastasis of CC and enhance sensitivity to chemotherapy. Ji et al. [134] found that QKI promotes the occurrence of circSLC26A4. circSLC26A4 promotes the proliferation and invasion of CC cells.

RBP-La has been shown to be aberrantly overexpressed in various solid tumors. The current study found that it is also upregulated in CC tissues [135, 136]. When the La gene is knocked down in CC cells, cell proliferation is severely affected. The main reason for this phenomenon is that La promotes translation of the oncogene CCND1, which is a key factor in controlling the transition from G1 to S phase of the cell cycle [135].

The expression level of MSI-2 in CC is negatively correlated with the survival rate of patients [137]. MSI-2 promotes the proliferation, invasion, and migration of CC cells by activating Wnt/β-catenin and Notch signaling pathways [138]. Mithramycin A is an anti-tumor agent that inhibits MSI-2 expression and reduces proliferation, invasion, and spheroid formation of CC cells [138].

m6A modification-related RBPs also play important roles in CC. It has been found that m6A reader IGF2BP2 can interact with circRNA-circARHGAP12 in CC cells to bind FOXM1 mRNA, thus stabilizing FOXM1 mRNA. The combination of these molecules promotes the proliferation and migration of CC cells [139]. The lncRNA KCNMB2-AS1 is overexpressed in CC as an oncogene that can maintain the malignant phenotype of cancer cells. IGF2BP3 delays the degradation of KCNMB2-AS1 by binding to the m6A-modified KCNMB2-AS1, leading to increased KCNMB2-AS1 expression [140]. Wang et al. [141] found that YTHDF1 is highly expressed in CC. When knocking down YTHDF1, the proliferation, migration, and invasion of CC cells are inhibited. Therefore, they performed RIP-seq, meRIP-seq, and Ribo-seq co-sequencing analyses of CC cell lines with knockdown YTHDF1 and identified RANBP2 as its downstream target gene. This molecular mechanism suggests that YTHDF1 upregulates the expression of RANBP2, thus promoting the proliferation, migration, and invasion of CC cells. Wang et al. [142] found that lncRNA GAS5-AS1 interacts with the tumor suppressor GAS5 and enhances GAS5 stability by binding to the RNA demethylase ALKBH5, thereby inhibiting the proliferation, invasion, and migration of CC cells. RBM15 is a methylase of m6A. Zhang et al. [8] found that RBM15 affects the proliferation, invasion

Table 3. The roles of RBPs in endometrial cancer

RBP	Molecular axis	Function	Cellular phenotype/Clinical effect	Reference
HuR	Unknown	Oncogene	Proliferation, apoptosis	[145]
HuR	HuR/ER-α	Oncogene	Result in hormone-dependent endometrial cancer	[145]
Ccdc	Unknown	Unknown	Potential tumor marker	[146]
MEX3A	MEX3A/Wnt/β-catenin	Oncogene	Proliferation, invasion, migration	[147]
MSI-1	Unknown	Oncogene	Poor prognosis	[148]
MSI-1	Unknown	Oncogene	Apoptosis	[149]
IGF2BP1	ERK/IGF2BP1/SOX2	Oncogene	Proliferation	[150]
IGF2BP1	IGF2BP1/PEG10/PABPC1	Oncogene	Proliferation, invasion	[151]
YTHDF2	YTHDF2/IRS1/MMP9	Tumour suppressor gene	Proliferation, invasion, migration	[152]
ALKBH5	ALKBH5/IGF1R/COL1A1/MMP9	Oncogene	Proliferation, invasion, migration	[153]
ALKBH5	ALKBH5/SOX2	Oncogene	Proliferation, stemness	[154]

and migration of cervical cancer cells through JAK-STAT signaling pathway.

RBPs in EC

EC is one of the most common gynecological cancers with a high incidence in obese, perimenopausal, and postmenopausal women. The pathological types of EC are complex; however, endometrioid adenocarcinoma is the most common. Owing to the abnormal bleeding symptoms, most patients with EC can be diagnosed at an early stage and have a better prognosis with surgery-based treatments. However, patients with an advanced stage or poor differentiation have a worse prognosis. The molecular classification of EC can help predict prognosis and guide treatment; however, there are still some limitations. It is important to continue exploring the molecular mechanisms underlying EC to identify new therapeutic targets and predict prognosis. RBPs are important RNA regulators that play key roles in EC RNA metabolism. This section summarizes studies on the relationship between RBPs and EC (**Table 3**).

HuR is considered an oncogene with malignant transformation, and it promotes tumor growth and is metastable [143]. HuR is more common in poorly differentiated, advanced and ER-α positive EC [144]. When HuR is knocked down, proliferation is inhibited and apoptosis is induced in EC cells [144]. Additionally, HuR may regulate ER-α, which induces hormone-dependent EC [144].

Ccdc is a novel RBP whose expression is significantly upregulated in EC. Therefore, it is expected to serve as a biomarker for EC [145].

Using biomimetic analysis, Yang et al. [7] identified MEX3A as an RBP that plays an oncogenic role in EC and is associated with a poor prognosis. MEX3A pro-motes the proliferation, invasion, and migration of EC cells. Mechanistically, MEX3A promotes tumor progression by activating EMT and regulating the Wnt/β-catenin pathway via DVL3 [7].

High MSI-1 expression is associated with low survival rates in endometrial adenocarcinomas [146]. In addition, MSI-1 is an independent prognostic factor for endometrial adenocarcinoma [146]. Falke et al. [147] found that MSI-1 is overexpressed in EC, especially in cancer stem cells. MSI-1 knockdown promotes EC cell apoptosis, regulates cell cycle progression, and inhibits tumor growth in vivo.

m6A modification-associated RBPs also play important roles in EC. In EC cells, peptidyl arginine deiminase II promotes the phosphorylation of MEK1 to ERK1/2, which activates IGF2BP1 [148]. IGF2BP1 binds to the m6A site in the 3' UTR of SOX2 to prevent SOX2 mRNA degradation [148]. An abnormal increase of oncogene SOX2 maintains the proliferation of EC cells [148]. PEG10 promotes cell cycle progression, facilitates the proliferation and invasion of cancer cells and is overexpressed in a variety of cancers. In EC cells, IGF2BP1 recognizes the m6A site of the 3' UTR of PEG10 mRNA and recruits PABPC1 to enhance its stability of PEG10 mRNA, thus promoting PEG10 protein [149]. This cellular signaling pathway reveals another potential mecha-nism by which IGF2BP1 plays a role in EC. Hong et al. [150] found that YTHDF2 is highly expressed in EC, and that YTHDF2 overexpression significantly inhibits the proliferation, migration, and inva-

sion of EC. YTHDF2 reduces MMP9 expression by promoting the degradation of IRS1 mRNA, inhibiting IRS1 expression, and suppressing the IRSI/AKT signaling pathway, thus inhibiting EC cell invasion. Pu et al. [151] found that ALKBH5 is significantly upregulated in EC and promotes EC cell proliferation and invasion. In terms of molecular mechanisms, ALKBH5 can remove m6A methylation on IGF1R mRNA to enhance its stability and promote IGF1R expression, which leads to the activation of the IGF signaling pathway. Activation of the IGF signaling pathway induces the expression of COL1A1 and MMP9, thus increasing the invasion and migration of EC cells [151]. Hypoxia accelerates cancer stem cells growth and tumor progression. Chen et al. [152] found that hypoxia leads to increased expression of ALKBH5 and SOX2, which contributes to the accelerated proliferation and maintenance of EC cell stemness.

Conclusion and future directions

Owing to breakthroughs in research techniques, researchers have discovered numerous RBPs. A large-scale study found that more than 10,000 RNA elements are bound by RBPs in the human genome and showed that these elements are associated with different cell types, tissue types, and developmental stages [153]. RBPs play an indispensable role in the human life process, have strong binding functions and can play corresponding roles by forming complexes with proteins or directly binding to various RNAs. Therefore, RBPs form a complex regulatory network in cells. Abnormal RBP levels can lead to various diseases. An increasing number of studies have shown that RBPs play a dual role in promoting and inhibiting cancer and that their abnormal changes play a key role in tumor development. RBPs are involved in the development of various malignancies through genomic alterations, transcriptional and post-transcriptional regulation, and post-translational modifications. In terms of bio-logical function, RBPs can regulate proliferation, apoptosis, invasion, metastasis, and chemosensitivity of cancer cells. In addition, more and more studies have found that RBPs are related to the DNA Damage Response of cancer cells [154].

Many studies have performed differential analyses of RBP-related genes, suggesting that RBPs may be potential markers for diagnosis and prognosis. For example, the upregulated expression of IGF2BP1 and ESRP1 is associated with poor prognosis in OC [155, 156], and IGF2BP3 is associated with poor survival in OC [115]. Increased FUBP1 expression is a negative factor for CC prognosis [157]. In addition, in-depth studies of the target genes and signaling pathways of RBPs could help reveal RBP-related small-molecule inhibitors or other novel drugs for cancer treatment. Several anti-tumor drugs targeting RBPs have been discovered and developed [158]. For example, MS-444, a drug that targets HuR, inhibits the binding of HuR to RNA, thereby reducing the proliferation and survival of cancer cells [159]. Pladienolide B is a drug that targets SRSFI and inhibits its binding to RNA, thereby affecting splicing and transcription in cancer cells [160], and it has shown inhibitory effects on multiple cancer cells, including lung cancer, pancreatic cancer, and OC [160]. LNA-IGF2BP3 is a chemically modified antisense oligonucleotide that inhibits IGF2BP3 binding to RNA, thereby reducing cancer cell invasion and migration [161]. It can be seen that RBPs have potential as cancer therapeutic targets. But targeting RBPs for cancer has some challenges and limitations. There are a large number of cancer-related RBPs and the structure of RBPs is complex, so it takes a lot of efforts to develop accurate and effective targets for RBPs [156]. RBPs are widely expressed in tissues and have a variety of functions. When targeting RBPs to treat cancer, it may have an impact on normal cellular processes, and the toxicity and safety of drugs need to be paid attention to. In addition, delivering drugs to specific tumor sites is an important problem to overcome. Therefore, developing an effective delivery system is key to the success of treatment. This requires the design of appropriate carriers, or nanoparticles to ensure that the therapeutic substance can be stably transported and released in the body. Overcoming these challenges requires further research and technological innovation to ensure that therapeutic strategies targeting RBP can be safely and effectively applied in clinical practice.

Gynecological malignancies remain a significant threat to women worldwide; there-fore, early diagnosis and effective treatment are essential. In this review, we introduce relevant studies on RBPs in gynecological cancers, which elucidate the mechanism of gynecological

tumorigenesis from a new perspective. RBPs are involved in multiple biological processes in gynecological cancers and have the potential to become biomarkers for the diagnosis and prognosis of gynecological tumors as well as potential therapeutic targets for the treatment of gynecological tumors. In order to translate the results of RBPs research into clinical applications, there are some key issues that need to be clarified or resolved. First, the regulatory networks of RBPs are complex. To comprehensively elucidate the mechanisms of RBPs in certain cancers, a more comprehensive understanding is needed. Most current studies have focused on the application of RBPs in one signaling pathway or one target gene. Second, a recent study applied the enhanced RNA interactome capture (eRIC) method to assess organ RBPs and found significant differences in the distribution and activity of RBPs between mammalian organs and cultured cells in vitro [162]. In addition, this study found that metabolic enzymes are more widely present in mouse organs as RBPs than in cells [162]. Significant differences in the expression levels of RBPs occur at the organ and cellular levels, and the reasons and mechanisms for these differences must be further explored. In addition, the functions of RBPs need to be fully elaborated. Although RBPs are known to bind to RNA, whether RBPs can form complexes with proteins and subsequently act on proteins must be determined. Finally, the translation of RBPs and downstream target genes identified in this study into clinically available biomarkers or effective therapies must be further explored. In summary, although our understanding of RBPs is limited, we believe that with continuous breakthroughs in technology, we will discover more RBPs, identify their roles, and apply the research results to clinical practice.

Acknowledgements

The authors acknowledge and appreciate our colleagues for their valuable efforts and comments on this paper. The authors gratefully acknowledge the financial support by Health Commission of Jilin Province (A project to improve the ability to diagnose and treat gynecological oncology; grant no. 3D517EC03427), Health Commission of Jilin Province (CBCT bone registration was used to analyze the effect of volume rotation intensity modulation on target dose; grant no. 2020SCZT012), Health Commission of Jilin Province (Dose-effect analysis of Zeiss intraoperative radiotherapy machine irradiating primary cultured vertebral metastases; grant no. 2019SCZT029).

Disclosure of conflict of interest

None.

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